

Adipose tissue metabolism and cardiometabolic health in obesity

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SUMMARY

Obesity is associated with an increased risk for metabolic impairments and chronic diseases, including insulin resistance, type 2 diabetes and cardiovascular diseases. Strategies to reduce body weight and obesity-related comorbidities include dietary (as discussed in **Chapter 2**), pharmacological and physical activity interventions. This thesis describes the effects of a pharmacological intervention as well as physical exercise interventions to improve metabolic health in obese individuals, with a focus on adipose tissue metabolism.

An increased renin-angiotensin system activity and a lower activity of the natriuretic peptide system have been linked to the development of type 2 diabetes and cardiovascular disease. Combination therapy with sacubitril/valsartan, a combined angiotensin receptor blocker (ARB) and neprilysin (NEP) inhibitor, facilitates the beneficial effects of the natriuretic peptide system, while inhibiting the detrimental effects of the renin-angiotensin system.

In **Chapter 3**, we performed a multi-centre, randomized, double-blind, double-dummy, parallel-group study to assess the effects of 8 weeks treatment with sacubitril/valsartan as compared to amlodipine on whole-body insulin sensitivity, determined by a hyperinsulinemic-euglycemic clamp in 98 obese hypertensive patients. We found that sacubitril/valsartan significantly improved peripheral insulin sensitivity without affecting body weight or waist circumference. Furthermore, abdominal subcutaneous adipose tissue lipolysis at rest was slightly but significantly increased in the sacubitril/valsartan as compared to the amlodipine group. Surprisingly, the increased subcutaneous adipose tissue lipolysis at rest did not translate into significant changes in whole-body lipolysis, as measured using the stable isotope [1,1,2,3,3-²H]-glycerol. Moreover, we also found no significant changes in total energy expenditure and substrate oxidation in resting conditions.

In **Chapter 4**, we extended the outcome of this multi-centre trial by investigating the effects of sacubitril/valsartan on abdominal subcutaneous adipose tissue and whole-body lipolysis as well as energy metabolism and substrate oxidation during a single bout of moderate-intensity aerobic exercise, which is known to stimulate lipolysis. We observed no significant effects of sacubitril/valsartan as compared to amlodipine on abdominal subcutaneous adipose tissue lipolysis, whole-body lipolysis, energy expenditure and substrate oxidation. Therefore, it seems that sacubitril/valsartan had no physiological relevant effects on adipose tissue lipolysis, whole-body lipolysis and substrate utilization.

To obtain more detailed insight into possible mechanisms underlying the findings described in Chapters 3 and 4, we assessed the effects of sacubitril/valsartan on abdominal subcutaneous adipose tissue gene expression patterns using microarray analysis and determined adipose tissue protein expression profiles in **Chapter 5**. We showed no significant changes in expression of genes and proteins of factors involved in lipolysis, natriuretic peptide signalling and mitochondrial oxidative metabolism.

Collectively, these data indicate that alterations in abdominal subcutaneous adipose tissue lipolysis, whole-body lipolysis or whole-body substrate oxidation at rest and during exercise, do not seem to contribute to the sacubitril/valsartan-

induced improvement in peripheral insulin sensitivity. It remains to be established whether sacubitril/valsartan has effects on other key metabolic organs, which may underlie the observed improvement in peripheral insulin sensitivity.

Beside pharmacological therapy, changes in lifestyle are effective in preventing the development of type 2 diabetes and related cardiometabolic complications. There is some evidence, mainly from rodent studies, that exercise training may improve adipose tissue function, thereby reducing obesity-related insulin resistance and other comorbidities. However, human studies that investigated the effects of exercise training on adipose tissue function are limited. Therefore, a second objective of this thesis was to determine the effects of physical exercise training on abdominal subcutaneous adipocyte morphology, adipose tissue gene and protein expression of markers related to adipose tissue function and *ex vivo* adipocyte lipolysis in metabolically healthy and metabolically compromised individuals.

In **Chapter 6**, we investigated the effects of a 12-weeks supervised, progressive, combined endurance and resistance exercise training program on insulin sensitivity and adipose tissue function in metabolically healthy and metabolically compromised sedentary, middle-aged men. We found that 12 weeks of exercise training improved body composition, physical fitness and peripheral insulin sensitivity, as assessed by a two-step hyperinsulinemic-euglycemic clamp. However, no significant effects on hepatic and adipose tissue insulin sensitivity, abdominal subcutaneous adipocyte morphology, adipose tissue gene and protein expression of markers related to adipose tissue function, nor β_2 -adrenergic sensitivity of abdominal subcutaneous adipose tissue lipolysis were observed in obese subjects, irrespective of their baseline metabolic status. Importantly, since we observed only a slight but significant decrease in fat mass, it is likely that a more pronounced decrease in adipose tissue mass is needed to induce significant changes in adipocyte morphology and, consequently, adipose tissue metabolism.

Also, since atrial natriuretic peptide (ANP) increases during exercise and plays an important role in adipose tissue lipolysis, we investigated abdominal subcutaneous adipose tissue (non-)adrenergically-mediated lipolysis before, during and after a single bout of endurance exercise and after 12-weeks of exercise training in metabolically healthy and metabolically compromised individuals in **Chapter 7**. Therefore, we investigated the effect of local combined α - and β -adrenoceptor blockade on local subcutaneous adipose tissue lipolysis at rest, during low-intensity endurance-type exercise and during recovery from exercise in sedentary, middle-aged obese insulin sensitive, obese insulin resistant and age-matched lean insulin sensitive men. In addition, we investigated whether a 12-week supervised, progressive, combined endurance and resistance exercise training improved the metabolic profile in obese men and (non-)adrenergically-mediated abdominal subcutaneous adipose tissue lipolysis in obese insulin resistant individuals. We demonstrated a major contribution of non-adrenergically-mediated lipolysis during exercise in all groups. Furthermore, we showed that the exercise training intervention improved body composition, physical fitness and exercise-induced changes in circulating free fatty acids, lactate and adrenalin concentrations in both obese groups and insulin sensitivity in the obese insulin resistant group. However,

this was not accompanied by changes in adrenergically- and non-adrenergically-mediated lipolysis in the subcutaneous adipose tissue of obese insulin resistant individuals. Together, these data suggest that even after a substantial improvement in metabolic profile and body composition after a 12-week exercise intervention, lipolytic disturbances remain unaffected in subcutaneous adipose tissue of obese insulin resistant individuals. Optimized therapies are warranted to achieve enhancements in the regulation of subcutaneous adipose tissue lipolysis, especially in metabolically compromised individuals.

Combined, these data indicate that even after exercise-induced improvements in body composition, physical fitness and peripheral insulin sensitivity, changes in abdominal subcutaneous adipose tissue metabolism and function are lacking and will most likely occur only after a more pronounced decrease in adipose tissue mass. Currently, it remains to be established which exercise training duration and modality is most optimal to induce beneficial effects in abdominal subcutaneous adipose tissue.